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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/470,467	12/22/99	MARGOLSKEE R	AP-32225-070

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BAKER & BOTTS LLP
30 ROCKEFELLER PLAZA
NEW YORK NY 10112

EXAMINER	
JONES, D	
ART UNIT	PAPER NUMBER
1619	

DATE MAILED: 11/08/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Best Available Copy

Office Action Summary	Application No.	Applicant(s)	
	09/470,467	MARGOLSKEE ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31, 34, 37, 39,-41, 44, 47, 49-52, 55, 58, and 60-63* is/are rejected.

7)☒ Claim(s) *32,33,35,36,38,42,43,45,46,48,53,54,56,57,and 59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

APPLICANT'S INVENTION

1. Applicant's invention is directed to composition, methods, and uses thereof wherein the compositions comprise a bitter tastant and a bitterness inhibitor.

COMMENTS/NOTES

2. After reconsidering the restriction requirement, the restriction requirement has been WITHDRAWN.

112 REJECTIONS

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, line 8: The claim as written is ambiguous because it is unclear what Applicant intends by the phrase 'the conditions are essentially the same'. It is unclear what changes, the temperature, amount of substance added, or so forth. One cannot ascertain which parameters remain the same and which vary. Please clarify.

103 REJECTIONS

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-31, 34, 37, 39, 40, 41, 44, 47, 49-52, 55, 58, and 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLaughlin et al (1993, Ciba Foundation Symposium, Vol. 179, pages 186-200) in view of Naim et al (1994, Biochem. J., Vol. 297, pages 451-454), Ruiz-Avila et al (1995, Nature, Vol. 376, pages 80-85), Spielman (1998, J. Dent. Res., Vol. 77, No. 4, pages 539-544), and Boughter et al (1997, The Journal of Neuroscience, Vol. 17, No. 8, pages 2852-2858).

McLaughlin et al disclose the bitter compound denatonium and that it raises the intracellular calcium concentration in rat taste cells by a G-protein mediated increase in inositol triphosphate (see entire document, especially, abstract). In addition, McLaughlin et al disclose the cloning of G-protein subunits (page 189, first and second complete paragraphs). On page 194, a proposed mechanism for bitter taste transduction is disclosed. Bitter compounds bind to and activate specific receptors which activate taste cell specific G-proteins. The activated G-alpha subunit possibly regulates the activity of phospholipase C leading to inositol triphosphate. Furthermore, the reference discloses that transducin and gustducin both play roles in bitter taste transduction to stimulate bitter receptors which may activate transducin and/or

gustducin. Thus, resulting in the removal of the inhibition of phosphodiesterase and leading to breakdown of taste cell cAMP. Hence, the net effect of lower cAMP levels would hyperpolarize the taste cell. Phosphodiesterase activation would be antagonistic to sweet activated adenylate cyclase; thus, leading to bit6ter opposition to sweet at the taste cell or taste bud level. McLaughlin et al fail to disclose various bitter tastants which activate transducin, trypsin sensitivity to monitor G-protein activation, and in vivo use bitter taste compositions for identifying bitter inhibitors.

Naim et al disclose amphipilic sweeteners and a bitter compound, quinine, which activate transducin and other G-proteins. Various compounds such as azolectin, mastoparan, sodium saccharin, sodium cyclamate, aspartame, neohesperidin dihydrochalcone (NHD), naringin, quinine chloride (hydrochloride), and sucrose were utilized (see entire document, especially, abstract; pages 451-452, 'Materials and Methods'; and page 452, Figure 1).

Ruiz-Avila et al disclose the coupling of a bitter compound, denatonium, to taste cell receptors which result in the activation of transducin. In addition, the reference discloses the use of trypsin sensitivity and GTP gamma-S-binding to monitor activation of transducin by rhodopsin. Furthermore, Ruiz-Avila et al disclose that only the bitter compound, denatonium, activated transducin and quinine and saccharin did not activate transducin (see entire document, especially, abstract; pages 81-82, bridging paragraph; and page 83, column 1, first complete paragraph).

Spielman discloses gustducin and its role in taste. In particular, a mechanism of gustducin mediated bitter taste signal transduction is disclosed wherein the bitter

stimulant denatonium activates a cell surface receptor that is coupled to gustducin. Gustducin activates a taste specific phosphodiesterase which reduces the intracellular levels of camp or cGMP (see entire document, especially, abstract; page 541, Figure b). In addition, Spielman disclose various gustducin and bitter transduction models such as (a) channel blockage; (b) cell surface receptors; (c) direct activation of G-proteins; (d) phosphodiesterase activation; and (e) phosphodiesterase inhibition (pages 542-543, 'Gustducin and other bitter taste transduction models'). Furthermore, Spielman discloses that sucrose signal transduction is associated with G-proteins and the elevation of cAMP in various species (page 543, 'Gustducin and sweet taste').

Boughter et al disclose differential expression of alpha-gustducin in taste bud population of rats and hamsters. In addition, it is disclosed that in rodents there are difference in the sensitivity to sweet and bitter stimuli in different populates of taste buds (see entire document, especially, abstract).

It would have been obvious to modify the invention of McLaughlin et al using the teachings of Naim et al, Ruiz-Avila et al, Spielman, and Boughter et al and generate in vivo compositions and methods thereof for identifying a bitter taste inhibitor, and the steps set forth in the methods of identifying the bitter inhibitor because (1) McLaughlin et al disclose gustducin and transducin and proposed mechanisms for bitter taste transduction. (2) Naim et al disclose the use of sweeteners and a bitter tastant (quinine) which activate transducin. (3) Ruiz-Avila et al disclose the bitter compound (denatonium) which activates transducin. In addition, Ruiz-Avila et al disclose the use of trypsin sensitivity to monitor activation of transducin by rhodopsin. (4) Spielman

discloses that various gustducin and other bitter taste transduction models are known in the art and their mechanisms. Thus, the activation and inactivation of G-proteins are taught. (5) Boughter et al disclose that transducin of sweet and bitter tasting substances is known to involve G-proteins. In particular, Boughter et al is of significance because the reference discloses that in rodents, there is difference in sensitivity to sweet and bitter stimuli. Hence, the skilled practitioner in the art would recognize that in vivo studies are possible. Furthermore, it would have been obvious to one of ordinary skill in the art to utilize the steps of the independent method claims and compare the G-protein levels to determine which compounds inhibit bitter taste because in the cited references, compounds were tested and it was determined which substances resulted in enhanced G-protein levels (e.g., see Naim et al, page 452, Figure 1). Since each of the cited references disclose gustducin/transductin and/or bitter tastants and inhibitors and there in taste, the references may be considered to be within the same field of endeavor. Hence, the references are combinable.

CLAIM OBJECTIONS

7. Claims 32, 33, 35, 36, 38, 42, 43, 45, 46, 48, 53, 54, 56, 57, 57, and 59 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Note: The claims are allowable over the prior art of record because the prior art neither anticipates nor renders obvious the additional limitations present in the above-cited claims in conjunction with the claims of the respective independent claims.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached on (703) 308- 2328. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1619

November 2, 2001